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Oral Presentations

LO1: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-FINDING STUDY OF THE EFFICACY AND SAFETY OF NAMODENOSON (CF102), AN A3 ADENOSINE RECEPTOR (A3AR) AGONIST, IN TREATING NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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Background: Namodenoson, an A_3AR agonist, demonstrated improved liver function and pathology in a NASH preclinical model. **Methods:** This phase 2 randomized double-blind placebo-controlled dose-finding study investigated orally administered namodenoson in patients (pts) with NAFLD and serum ALT levels ≥60 U/L (including a subset with NASH). Pts were randomized (1:1:1) to receive namodenoson 25 mg BID, 12.5 mg BID, or placebo for 12 wks and were followed up until wk 16. Endpoints included efficacy parameters, safety profile, and study of relevant biomarkers. **Results:** The analysis included 60 pts. ALT levels decreased consistently during the study with namodenoson treatment in a dose-dependent manner (wk 12 mean change from baseline [CFB]:-14.6, -8.7, and -4.2 U/L in the 25 mg, 12.5 mg, and placebo groups, respectively; p=0.066 for 25 mg vs placebo); 37%, 24%, and 10% of pts in the 25 mg, 12.5 mg, and placebo groups, respectively, achieved ALT normalization at 16 wks (p=0.038 for 25 mg vs placebo). AST levels also decreased throughout the study in a dose-dependent manner (wk 12 mean CFB:-8.4, -5.9, and -0.8 U/L in the 25 mg, 12.5 mg, and placebo groups,

respectively; p=0.03 for 25 mg vs placebo). In addition, a significant improvement in adiponectin was noted (wk 12 mean CFB: 266, 559, and -137 ng/mL for 25 mg, 12.5 mg, and placebo, respectively; p=0.03 for 12.5 mg vs placebo). At wk 12, a significant decrease in liver fat volume (determined by MRI-PDFF) was observed with namodenoson (mean CFB: -159, -31, and -74 cm^3 for 25 mg, 12.5 mg, and placebo, respectively; p=0.03 for 25 mg vs placebo). In addition, a significant decrease in Fib4-scores was noted with namodenoson (wk 12 mean CFB: -0.28,-0.09, and -0.03 for 25 mg, 12.5 mg, and placebo, respectively; p=0.011 for 25 mg vs placebo) suggesting an inhibitory effect of namodenoson on fibrosis progression. A consistent dose-dependent decrease in body weight was recorded in all study groups over time (wk 12 mean loss from BL: 2.1, 1.6, and 0.5 kg in the 25 mg, 12.5 mg, and placebo groups, respectively). A_3AR expression levels were stable over time in all study groups. Namodenoson was well-tolerated at both doses with no drug-emergent severe adverse events and no hepatotoxicity. **Conclusion:** A_3AR is a valid target whose levels remain stable after chronic treatment. Namodenoson at 25 mg BID is safe and more effective than 12.5 mg BID.

LO2: SAFETY AND EFFICACY OF COMBINATION THERAPIES INCLUDING SEMAGLUTIDE, CILOFEXOR, AND FIRSOCOSTAT IN PATIENTS WITH NASH

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Background: Given the biological complexity of NASH, combining therapies with complementary mechanisms may provide optimal benefit. We evaluated the safety and efficacy of semaglutide (sema), a GLP-1 receptor agonist, alone and in combination with the FXR agonist cilofexor (CILO) and/or the ACC inhibitor firsocostat (FIR), in patients with NASH. **Methods:** This phase 2 trial randomized 108 non-cirrhotic patients with NASH (F2-F3 on biopsy, or MRI-PDFF ≥10% and liver stiffness by transient elastography [LS by TE] ≥7 kPa) to sema (n=21), sema+CILO 30 mg (n=22), sema+CILO 100 mg (n=22), sema+FIR 20 mg (n=22), or sema+CILO 30 mg+FIR 20 mg (n=21) for 24 weeks (W24). CILO and FIR were taken once daily and sema subcutaneously once weekly (dose escalated from 0.24 mg to 2.4 mg weekly over 16 weeks). The primary endpoint was safety; exploratory endpoints included changes in liver biochemistry, ELF, liver stiffness by TE, and MRI-PDFF between baseline (BL) and W24. Least square mean (LSmean) changes based on post-hoc ANCOVA models adjusted for BL value and diabetes status. **Results:** At BL, median (IQR) age and BMI were 54 yrs (48, 61) and 34.3 kg/m^2 (30.9, 39.4), respectively; 55% had diabetes. All regimens were well tolerated. The most common adverse events (AEs) were gastrointestinal; 5–14% discontinued any study drug due to AEs. Minimal pruritus was observed (5–10% in CILO groups only, all grade 1, no discontinuations). LSmean change in LDL from BL to W24 ranged from –9 mg/dL with sema to 7 mg/dL with sema+CILO+FIR, and 23 mg/dL with sema+CILO 100 mg; one sema+FIR-treated patient developed triglycerides ≥500 mg/dL. At BL, median ALT was 50 U/L (31, 82), MRI-PDFF was 17.9% (12.0, 24.3), and LS by TE was 9.3 kPa (7.7, 12.0). Greater LSmean reductions in ALT were observed with combinations vs sema at W24 (all p<0.05; **Fig**); reductions in AST (–26 to –11 U/L), GGT (–40 to –21 U/L), CK18 M30 (–312 to –179 U/L), and ELF (–0.59 to –0.42) were observed in all groups. From BL to W24, larger reductions in hepatic steatosis by MRI-PDFF were observed with combinations vs sema (**Fig**). At W24, LSmean reductions in liver stiffness by TE were: sema, –2.5 kPa; sema+FIR, –3.8 kPa; and sema+CILO+FIR, –3.5 kPa; a ≥25% reduction in liver stiffness was more common with combinations (53–63%) vs sema (33%). Changes in body weight were similar between groups (–7.0 to –9.6%). **Conclusion:** In patients with NASH, combinations of sema with CILO and/or FIR were well tolerated and may provide additional benefits vs sema monotherapy.